Abstract

This case report describes the signalment, diagnosis, and treatment of a 5-year-old dog experiencing an addisonian crisis. The purpose of this article is to outline the approach of the veterinary healthcare team in identifying and addressing a typical presentation of this medical emergency. Key takeaways include tips for identifying key clinical signs of Addison’s disease and a review of the recommended emergency and long-term treatment.
Hypoadrenocorticism, also called Addison’s disease, is an underproduction of glucocorticoids and mineralocorticoids by the adrenal glands. It is sometimes referred to as the “great pretender” because clinical signs are often nonspecific and can mimic those of other diseases. For patients exhibiting nonspecific clinical signs such as anorexia, lethargy, vomiting, and diarrhea, hypoadrenocorticism should be on the differential diagnosis list until proven otherwise. If the condition becomes serious (sudden weakness, severe vomiting and diarrhea, and sometimes collapse), it is called an addisonian crisis and is considered a medical emergency. Long-term prognosis for patients with hypoadrenocorticism is excellent with proper treatment; however, because damage to the adrenal glands is irreversible, treatment must continue throughout the patient’s lifetime. Pets predisposed to hypoadrenocorticism include middle-aged, female, mixed-breed dogs. Hypoadrenocorticism is rare in cats but has been documented. This article describes an addisonian crisis in a dog; the case was considered “textbook” with regard to clinical presentation, laboratory values, and signalment.

THE CASE

Presentation
Josie, a 5-year-old, spayed female Chihuahua mix was brought to our hospital due to anorexia, lethargy, polydipsia, shaking, and vomiting. She seemed depressed and weak. Physical examination revealed bradycardia at 40 beats per minute (reference range, 70 to 120 bpm), mild hypothermia at 99.5 °F (reference range, 99.5 °F to 102.5 °F), and tacky mucous membranes indicating 5% dehydration. All other parameters were within normal limits.

Take-Home Points

- Hyperkalemia and hyponatremia are pathognomonic for hypoadrenocorticism.
- Calcium gluconate is cardioprotective and antagonizes the effects of potassium on the heart.
- Dextrose, insulin, albuterol, and sodium bicarbonate are all options for treating hyperkalemia.
- Adrenocorticotropic hormone stimulation testing is the gold standard for diagnosing hypoadrenocorticism.
- Damage to the adrenal glands is irreversible.
- Long-term treatment consists of glucocorticoid and mineralocorticoid replacement.
Diagnostic Testing
After an IV catheter was placed, blood was obtained for a minimum database. Packed cell volume was 53% (reference range, 37% to 55%), and total solids were 4.5 g/dL (reference range, 5.4 to 7.1 g/dL). Blood glucose was 96 mg/dL (reference range, 67 to 132 mg/dL), and lactate was 1 mmol/L (reference range, 0.5 to 2 mmol/L). Noninvasive Doppler measurement indicated normal systolic blood pressure of 160 mm Hg (reference range, 150 ± 20 mm Hg). An electrolyte panel revealed severe electrolyte abnormalities, including hyperkalemia at 6.9 mEq/L (reference range, 3.5 to 5 mEq/L) and hyponatremia at 129 mEq/L (reference range, 138 to 148 mEq/L). These abnormalities are pathognomonic for hypoadrenocorticism. As a result, blood was submitted for an adrenocorticotropic hormone (ACTH) stimulation test.

An electrocardiogram, obtained due to the bradycardia, revealed atrial standstill, which can result from hyperkalemia. Atrial standstill is a transient bradyarrhythmia characterized by lack of atrial depolarization (FIGURE 1). Hyperkalemia decreases cardiac resting membrane potential, thus increasing cardiac excitability. Typically, atrial standstill is not observed until potassium concentration exceeds 8.5 mEq/L; however, as Josie’s case demonstrates, it can occur at lower concentrations.

Initial Treatment
For cardioprotective effect, calcium gluconate (10%) was administered slowly at 1 mL/kg IV while the electrocardiogram was monitored. Calcium gluconate does not affect potassium levels but instead antagonizes potassium’s effect on cardiomyocytes. Treatment should be slowed or stopped if further bradycardia or other arrhythmias develop.

To lower potassium levels, 1 mL/kg 50% dextrose diluted to 25% and 1 unit of regular insulin were

FIGURE 1. Electrocardiogram demonstrating atrial standstill.
administered IV. Dextrose increases endogenous insulin release, pushing potassium into cells. Because of its hyperosmolarity, dextrose should be diluted to at least 25% to reduce the risk for peripheral phlebitis. Insulin administration further promotes intracellular potassium exchange. Serial monitoring of blood glucose, with or without dextrose supplementation, is essential after administration of insulin to avoid iatrogenic hypoglycemia.

Alternative therapies for reducing hyperkalemia include sodium bicarbonate or albuterol. Sodium bicarbonate (1 to 2 mEq/kg), an alkalizing agent, exchanges hydrogen ions for potassium. The effect is slower than that of alternative therapies and affects acid–base status. Albuterol (1 puff), a β-adrenergic agonist, stimulates the sodium–potassium pump by pushing potassium intracellularly. Because hypoglycemia is not a side effect, albuterol and sodium bicarbonate are especially suitable if outpatient care is the only realistic option for the cost-conscious client.

**Intensive Care**

After Josie’s initial crisis was controlled, she was admitted to the intensive care unit, where IV crystalloid fluid therapy was started at 120 mL/kg/day, twice the maintenance dosage. Lactated Ringer’s solution was used because it is potassium deficient (4 mEq/L). Physiologic sodium chloride could also be considered because it is potassium free; however, caution must be taken to not increase sodium values too quickly. Rapid changes in sodium can cause cerebral edema and result in severe neurologic changes. The sodium concentration of 0.9% sodium chloride is 154 mEq/L compared with 130 mEq/L in lactated Ringer’s solution. Dextrose 2.5% was added to the IV fluids to preemptively treat iatrogenic hypoglycemia from insulin administration. Dextrose supplementation was discontinued after 6 hours because Josie was hyperglycemic (glucose 172 mg/dL).

While hospitalized, Josie received maropitant at 1 mg/kg IV q24h, steroid replacement with dexamethasone-SP at 0.2 mg/kg IV q24h, and 1 subcutaneous injection of deoxycorticosterone pivate (DOCP) at 2.2 mg/kg. Josie did not experience any vomiting and ate voluntarily within 10 hours of presentation. Her IV glucocorticoid steroid was transitioned to oral prednisone 2.5 mg (0.6 mg/kg) q24h.

ACTH results of <1 µg/dL (precortisol reference range, 1 to 6 µg/dL, and postcortisol reference range, 7 to 17 µg/dL) indicated hypoadrenocorticism. Subsequent serial electrolyte panels revealed an initial potassium spike followed by a steady decrease (TABLE 1). After receiving proper fluid therapy, steroid replacement, and gastrointestinal support, Josie improved. She began eating and had no episodes of vomiting.

**Long-Term Treatment**

After 2 days of hospitalization, Josie’s condition was stable and she was discharged. Discharge instructions included prednisone at 2.5 mg PO q24h for 3 days, tapered to a physiologic dose of 1.25 mg (0.3 mg/kg) PO q24h. Josie was also scheduled to receive a DOCP injection 1 month later. She was currently receiving this same regimen of daily prednisone and monthly DOCP at the time of publication.

**DISCUSSION**

The adrenal glands, situated cranial to the kidneys,
Cortisol helps regulate blood pressure, blood volume, and blood glucose levels. During times of stress, cortisol is released in larger amounts.

produce mineralocorticoids, corticosteroids, and sex hormones within the outer cortex and catecholamines within the central medulla.

Cortisol, the primary glucocorticoid, is regulated by a negative feedback loop. The hypothalamus releases corticotropin-releasing hormone, signaling the anterior pituitary to release ACTH, which then tells the adrenal cortex to release cortisol. When physiologic cortisol levels are reached, the adrenal cortex signals back to the anterior pituitary and hypothalamus to stop releasing corticotropin-releasing hormone and ACTH. Cortisol helps regulate blood pressure, blood volume, and blood glucose levels. During times of stress, cortisol is released in larger amounts.

Aldosterone, the primary mineralocorticoid, is responsible for normovolemic and electrolyte homeostasis by sodium, chloride, and water absorption and potassium excretion. Low aldosterone levels decrease the glomerular filtration rate, which then stimulates the renin-angiotensin-aldosterone system (FIGURE 2).

Although the exact etiology is unknown, primary hypoadrenocorticism is commonly accepted to result from immune-mediated destruction of the adrenal cortex. Other causes of adrenal destruction include neoplasia, trauma, infectious infiltrates, hemorrhage, hypoperfusion, and iatrogenesis. Secondary

FIGURE 2. Renin-angiotensin-aldosterone system. ACE=angiotensin-converting enzyme; ADH=antidiuretic hormone.
hypoadrenocorticism results from pituitary or hypothalamic dysfunction, frequently associated with exogenous steroid withdrawal.¹

To diagnose hypoadrenocorticism, the gold standard is ACTH stimulation testing. To perform this test, a baseline serum sample is obtained for a resting cortisol value. Next, 5 µg/kg of cosyntropin, a synthetic molecule that mimics the effects of ACTH, is administered intravenously.¹¹ One hour later, a second serum sample is obtained for a post-ACTH cortisol value. An absent-to-minimal response, such as Josie’s, indicates insufficient adrenal activity, consistent with hypoadrenocorticism. Results can be inaccurate if synthetic steroids (e.g., prednisone) cross-react with the assay. However, for patients in an addisonian crisis, early steroid therapy is necessary to control clinical signs. For these patients, dexamethasone should be used because it does not cross-react with cortisol and usually will not affect results.¹²

Diagnostic abnormalities associated with hypoadrenocorticism include prerenal azotemia, hyposthenuria (<1.03), and a sodium:potassium ratio of less than 28:1 (reference range, 27:1 to 40:1).¹³ Although within the reference range, a ratio of 28:1 is still 95% accurate for classifying hypoadrenocorticism.¹³ Patients with atypical cases of hypoadrenocorticism can have sodium and potassium levels within normal limits. These cases result from glucocorticoid insufficiency only and affect up to 30% of dogs with hypoadrenocorticism.¹²

Treatment of hypoadrenocorticism includes glucocorticoid and mineralocorticoid replacement. For glucocorticoid replacement, dexamethasone and prednisone or prednisolone are commonly used. Dexamethasone-SP (0.1 to 0.2 mg/kg loading dose, followed by 0.05 to 0.1 mg/kg IV q12h) is used initially until oral medications are tolerated. Prednisone is then administered at 0.1 to 0.2 mg/kg daily and tapered to the lowest dose possible. Side effects of glucocorticoids include polyuria, polydipsia, polyphagia, weight gain, poor hair coat, vomiting, diarrhea, and hepatopathy.

For mineralocorticoid replacement, DOCP is administered at 1.6 to 2.2 mg/kg IM.¹⁴ Administration of DOCP is recommended every 3 to 4 weeks;¹ however, a 2017 study concluded that the duration of action exceeds this recommended dosing schedule;¹⁵ which can thus be made more cost-effective by individualizing the dosing interval. As treatment for hypoadrenocorticism is lifelong, financial limitations play a major role in a client’s decision to treat. While determining an individual dosing interval, close attention to emerging clinical signs and electrolyte monitoring are crucial. An oral alternative to DOCP is fludrocortisone, a potent mineralocorticoid supplement with glucocorticoid activity as well. Although clinically used for its mineralocorticoid effects, dogs receiving fludrocortisone may not require additional glucocorticoid supplementation.¹⁶ Dogs receiving both fludrocortisone and prednisone may exhibit signs of hyperadrenocorticism (e.g., polydipsia and polyuria).

References
CLEVOR®
(ropinirole ophthalmic solution)
30 mg/mL
For ophthalmic use in dogs only

Single use dropper

BRIEF SUMMARY: Before using CLEVOR® (ropinirole ophthalmic solution), please consult the product insert, a summary of which follows:

CAUTION:
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATION:
For induction of vomiting in dogs.

DOSE AND ADMINISTRATION:
This product should be administered by veterinary personnel.

Dosing Instructions:
Administer the appropriate number of eye drops topically according to Table 1. The number of eye drops administered corresponding to body weight results in a target dose of 3.75 mg/mL (dose band 2.7 - 5.4 mg/mL). If the dog does not vomit within 20 minutes of the first dose, then a second dose may be administered.

Dose Administration:
4 - 11.1 lbs (1.8 - 5 kg), 1 drop. Example: 1 drop into either left or right eye. 11.2 - 22.1 lbs (5.1 - 10 kg), 2 drops. Example: 1 drop into each eye. 22.2 - 44.1 lbs (10.1 - 20 kg), 3 drops. Example: 2 drops in one eye and 1 drop in the other eye. 44.2 - 77.2 lbs (20.1 - 35 kg), 4 drops. Example: 2 drops in each eye. 77.3 - 132.3 lbs (35.1 - 60 kg), 6 drops. Example: An initial dose of 2 drops in each eye, followed 3 minutes later by 1 drop in each eye. 132.4 - 200.5 lbs (60.1 - 100 kg), 8 drops. Example: An initial dose of 2 drops in each eye, followed 2 minutes later by 2 drops in each eye.

- Wear gloves and protective eye wear when handling or administering this product to prevent accidental exposure.
- Open the dropper by twisting off the tail.
- Keep the dog's head steady in a slightly upright position.
- Hold the dropper in an upright position without touching the eye.
- Rest your finger on the forehead of your dog to maintain the distance between the dropper and the eye.
- Squeeze the prescribed number of drops in to the eye(s).
- CLEVOR is a single use dropper and is light sensitive.
- After administration, with gloves on, return the dropper to the aluminum pouch and place in the carton.
- If the dog does not vomit, a second dose can be given 20 minutes after administration of the first dose.

This second dose is the same number of drops as the first dose.

Thirty minutes after opening, with gloves on, dispose of dropper, aluminum pouch, and carton.

Refer to the Animal Safety Warnings section for treatment of protracted vomiting.

CONTRAINdications:
Do not use in dogs with central nervous system depression or seizures.
Do not use in cases of ingestion of sharp foreign objects, corrosive agents (acids or alkalis), volatile substances or organic solvents.
Do not use in cases with corneal ulceration, ocular irritation, or ocular injury.
Do not use when there is a known sensitivity to ropinirole or the inactive ingredients.

WARNINGS:
Human Safety Warnings:

Avoid contact with the product if pregnant, planning to become pregnant, or breast-feeding, as accidental exposure. In case of accidental eye, oral or skin exposure, flush with water. If wearing contact lenses, lenses should be removed first, then continue rinsing.

Animal Safety Warnings:
This product should be administered by veterinary personnel.

Dogs should be monitored for CLEVOR-associated clinical signs, including protracted vomiting, salivation, muscle tremors, evidence of abdominal discomfort, lethargy, transient tachycardia, transient decrease in blood pressure and signs of ocular irritation, including conjunctival hyperemia, mild blepharoconclusion, and protrusion of the third eyelid. These clinical signs are related to the pharmacological action of ropinirole. To stop protracted vomiting, administer metoclopramide (dopamine D2 antagonist) at a dose of 0.5 mg/kg intravenously (IV) or subcutaneously (SQ). Metoclopramide also decreases the prevalence of most CLEVOR associated clinical signs.

PRECAUTIONs:
The safe use of CLEVOR has not been evaluated in dogs with cardiac disease or cardiovascular compromise. CLEVOR can cause transient tachycardia and transient decreased systolic blood pressure.
The safe use of CLEVOR has not been evaluated in dogs with hepatic impairment. CLEVOR is metabolized by the liver.
The safe use of CLEVOR has not been evaluated in dogs younger than 4.5 months of age and weight less than 4 pounds.
The safe use of CLEVOR has not been evaluated in dogs that are pregnant, lactating, or intending to breed.

ADVERSE REACTIONS:
Safety was evaluated during a field study that enrolled 132 dogs (100 in the CLEVOR group and 32 in the vehicle control group). CLEVOR was administered as drops into the eyes at the dose as directed in the dosing table (see DOSAGE AND ADMINISTRATION). The following table shows the number of dogs exhibiting ocular, systemic, and clinical pathology adverse reactions.

ADVERSE REACTIONS Reported During the Study (all dose groups): Ocular adverse reactions included conjunctival hyperemia, protrusion of the third eyelid, conjunctival discharge, blepharoconclusion, conjunctival swelling, corneal ulceraion and corneal fluorescein uptake without corneal ulceration. Systemic organ system were lethargy, tachycardia (>160 beats per minute), vomiting duration longer than one hour, salivation, trembling, diarrhea or soft stool, anorexia and borborygmi. Clinical pathology organ systems were crystalluria, pyuria, increased liver enzymes, decreased blood glucose and increased prothrombin time.

To report suspected adverse events call 1(800) 835-9496, for technical assistance or to obtain a copy of the SDS, contact Vetoquinol USA, Inc. at 1 (800) 267-5707 or www.vetoquinolusa.com.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalai.

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